CLINICAL PRACTICE

The development of Clinical Guidelines for the use of Zuclopenthixol Acetate

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Objective: *This paper illustrates the process that was undertaken in the development of guidelines for the use of Zuclopenthixol Acetate (ZA) and presents the guidelines that were developed at the end of this process.*

Conclusions: *A number of investigations were undertaken to inform the above process, including: (i) A questionnaire sent to College Fellows and psychiatric registrars, to assess their use of ZA in the management of acute arousal in psychosis. This highlighted the lack of confidence that clinicians had in using ZA and some deficits in knowledge that confirmed the local need for such guidelines; (ii) A retrospective audit of the use of ZA in two psychiatric intensive care units over a 6 month period. This revealed significant differences between the centres in the manner in which ZA was prescribed; (iii) A review of published studies on ZA.*

Key words: *clinical guidelines, zuclopenthixol acetate.*

INTRODUCTION

The important role that medications play in controlling aroused and aggressive behaviour associated with acute psychosis is an accepted fact of modern psychiatric care. Over the years, the terminology for this practice has varied, from "chemical restraint" to the preferred term of "rapid tranquillisation".[1] Guidelines for the use of medication in this way have been developed and published in a variety of settings,[2,3] but we are aware of no published guidelines specifically for the use of Zuclopenthixol Acetate (ZA). ZA is unique in the psychopharmacological armamentarium in that it is essentially a short-acting depot formulation, with efficacy for 24–48 hours after administration. The utility in the intensive care setting is that it obviates the need for the repeated intramuscular administration of medication often required to deal with acute arousal in patients with psychosis.

WHAT ARE THE BENEFITS OF GUIDELINES?

Over the past 50 years, clinicians have been presented with a widening choice of medications which can be used in acute psychotic arousal. The guidelines that do exist in this area rationalise the choice somewhat, mostly recommending the combination of high potency neuroleptics and benzodiazepines.[2,4–7] However, this still leaves a rather overwhelming array of potential combinations.

Junior medical staff are often the ones involved in the prescription of rapid tranquillisation medications, often in the context of having to respond to a critical event. Such situations are often tense and anxiety provoking. Guidelines can be useful tools to assist medical staff in these situations and can help to ensure that the intervention is based on best practice standards. Other benefits include the potential reduction of

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untoward events such as respiratory depression and acute extra-pyramidal side effects (EPSE).

Rationalising the types of medications used in these emergency situations also assists nursing staff by allowing them to become expert in the use of a few medications, and familiar with their efficacy and side effect profile. This builds confidence, which in turn assists staff in coping in these high stress environments.

ESTABLISHING A NEED FOR SPECIFIC GUIDELINES FOR USE OF ZA

A two-stage design was adopted to ascertain current knowledge about, and use of, ZA in Western Australia (WA). First, a questionnaire was sent to all College Fellows and psychiatric trainees in WA. This asked a series of questions regarding their knowledge about the management of acute arousal and in particular the effects of, and how to use, ZA. The response rate was 36% (84/236) with 34% of respondents being registrars and 61% Fellows. The commonest area of practice was in the public arena (59%) with those in purely private practice making up a further 21%.

When asked how they would use ZA, 80% of respondents stated they would administer it as a single "once off" medication targeting acute verbal and physical aggression. This is contrary to the recommendations from the manufacturer, and to the guidelines given in prescribing manuals, which suggest a course of injections is usually optimal.[8–10] Just under half (n = 40) of the respondents routinely gave ZA with another psychoactive medication, most frequently a benzodiazepine (clonazepam being most frequently used). Sedation was cited as being the most frequent side effect of ZA, and although EPSE were recognised as a complication of treatment, respondents rated this as relatively uncommon (on a linear scale of 1–5, mean score was < 3).

When asked how long a single intramuscular injection of ZA would take to bring about clinical benefit, the majority (67%) of respondents believed that this would occur in under 60 minutes; only 12% recognised that sedation continued to be exerted for up to 8 hours after its administration. Overall, the respondents recognised their lack of confidence in using ZA, and felt that clinical guidelines would be helpful in their clinical practice. The limited results shown here certainly illustrate the potential benefits in developing such guidelines.

As a separate exercise, we performed a retrospective audit of ZA use in the three psychiatric intensive care units (PICUs) in WA. Through pharmacy records, 103 patients were identified as having been administered ZA during the six-month review period. Examination of medical files and medication charts revealed that the range of the total amount of ZA prescribed during each inpatient stay was between 50 and 450 mg, with a mean total dose of 165 mg. Clinicians in Centre 1 gave significantly higher total doses (mean 208 mg *vs* 122 mg at the other two centres, combined; $F = 22.8$; $P < 0.05$), and were significantly less likely to use a course of treatment (56% *vs* 93%; $P < 0.05$). In around 50% of cases, ZA was administered on its own, while in the remainder another psychotropic agent was administered concomitantly; clonazepam was the most favoured adjunctive medication (34%). Again there were differences between the centres, with Centre 1 using more clonazepam and midazolam, and the other centres using clonazepam equally with droperidol as adjunctive treatment.

Thus, the audit revealed a lack of consistency in the use of ZA both within and between PICUs, and suggested ZA was not always being used in a manner consistent with best practice, nor based on the manufacturer's recommendations. This, in combination with the findings from the questionnaire study, suggested that clinical guidelines for the use of ZA would be helpful to clinicians, and might enhance consistency of use of this agent.

WHAT DOES THE LITERATURE SAY?

Specific guidelines on the use of ZA have been lacking despite recent comments in the literature that such guidelines would be useful.[11] Recommendations produced by the manufacturer focus on parameters such as dose range and frequency of administration, and although they give some guidance regarding which patients ZA should be used for, these are very broad, stating "acute psychosis".[12]

We conducted a literature review by identifying published papers available through Medline (1987–2000), using keywords "zuclopenthixol", "acuphase" "acute psychosis" and "review". The search revealed 14 articles. A number of the studies suffered from methodological problems such as small sample size, lack of control groups, and so on. However, as the current review focused on assisting the development of clinical guidelines, we incorporated findings from all of the studies, though gave weighting to the methodologically rigorous randomised controlled trials.[13] In sum, there was a reasonable consistency between trials on the following:

- Several studies suggested that, depending on the individual's diagnosis, a differential response to ZA can be expected. That is, those with an exacerbation of chronic psychotic illness or acute mania tended to show a more rapid response, evidenced by decline in clinical global impression (CGI) score ($P < 0.0001$)[8] and Bech Rafaelsen Mania scale (BRMAS) scores ($P < 0.001$).[8,14]

- There was reasonable agreement that the time of onset of sedation was between 15–90 minutes and that this level of sedation increases to reach a maximum after 8 hours. The sedative effect decreases with subsequent injections of ZA unless the dose is increased.
- Those individuals with mania and first episode psychosis were found to have less of a sedative response and took longer to show a sedative response as compared to those with a relapse of chronic psychosis.

The manufacturers warn of the risk of EPSE, dizziness and orthostatic hypotension. The way in which the studies were performed made direct comparisons of dose difficult and therefore complicates the analysis of incidence of side effects. Of note was one study by Lowert *et al.*[15] in which 21% of 70 males experienced an acute dystonic reaction (mean dose of ZA 70 mg). This reaction could be seen from up to 72 hours after the injection and this would raise concern about giving ZA in any setting other than in hospital.

CLINICAL GUIDELINES FOR ZUCLOPENTHIXOL ACUPHASE

In the Fremantle Hospital PICU, a process already existed for the management of acute arousal

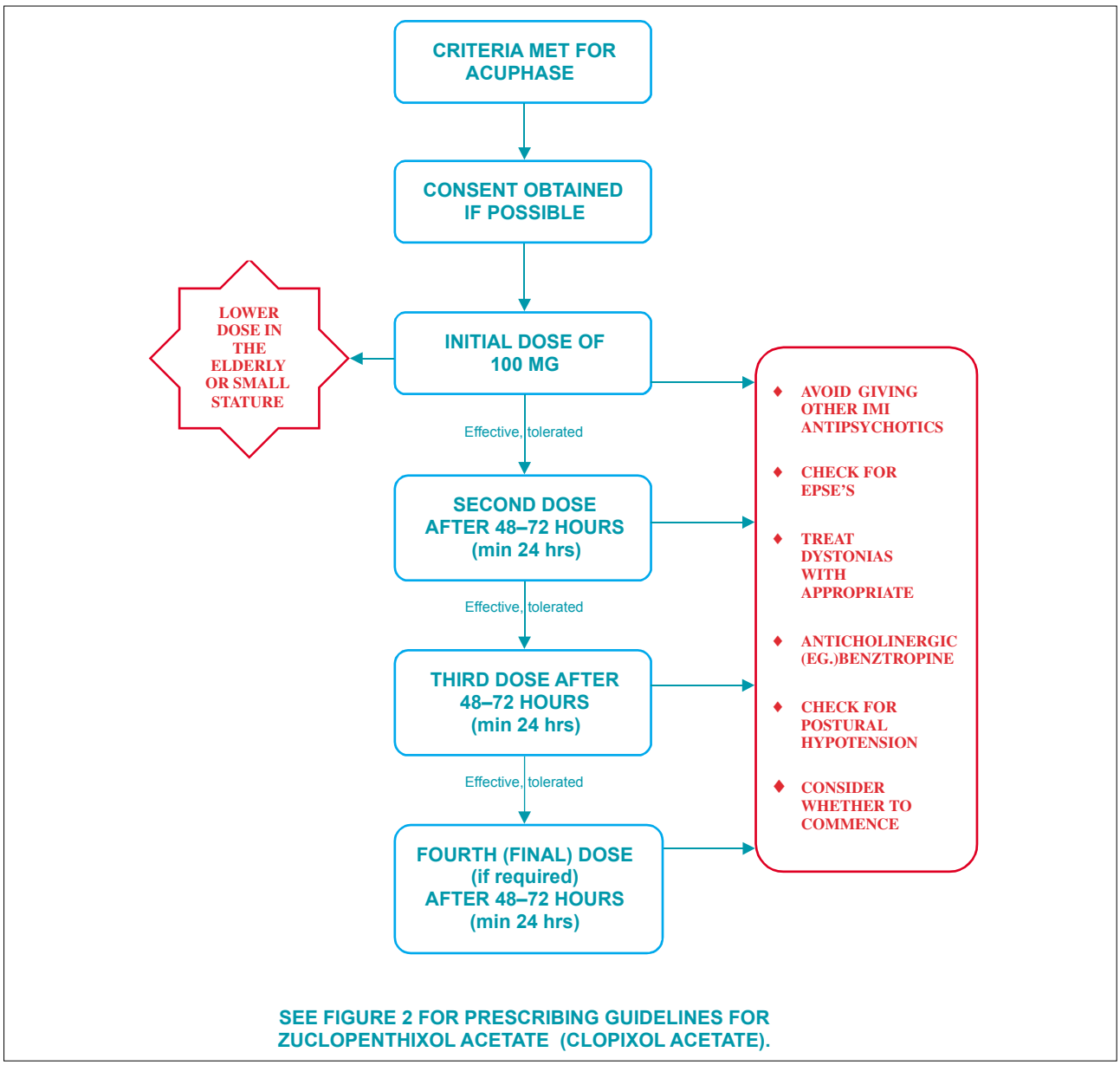

Figure 1: Alma Street guidelines for the use of Clopixol Acuphase (Zuclopenthixol Acetate).

Acuphase should be considered as a **treatment course** rather than simply a PRN ("as required") medication for acute arousal. An effort should be made, where feasible, to obtain verbal informed consent from the patient.

Acuphase should only be prescribed to patients who:

- Have required **other intramuscular injections (IMI)** of medication for acute arousal, **and**
- Have had **sufficient time for assessment of response and/or side effects** to previously injected drugs (minimum of 30-60 minutes);
- **Or** have previously received Acuphase and have shown a **good tolerability and response** to it.

Acuphase is not usually recommended for patients who are neuroleptic-naive

PRESCRIBING INFORMATION FOR ACUPHASE:

- Usual dose is **100 mg every 48–72 hours.**
- **Neuroleptic naive patients,** those of **small stature,** and **the elderly** may require lower doses **(25 or 50 mg) and careful clinical monitoring.**
- **Large young males** may require higher doses **(up to 150 mg).**
- A course of injections would usually be prescribed (e.g. 100 mg every 48–72 hours.) Maximum dose is **400 mg over two weeks or 4 injections (whichever comes first)**.
- At least **24 hours** must elapse between Acuphase injections.
- Review carefully for EPSE's and treat rigorously if they occur.
- Monitor blood pressure carefully (hypotension may occur).

Sedation may initially be seen between **15 and 90 minutes** after injection and **peaks after 8 hours**.

- **Effects last up to 72 hours.**
- **The first injection is usually the most sedating**
- Acuphase may need to be given with IMI lorazepam or midazolam if immediate sedation is required. (NB must be given separately, cannot be mixed in the same syringe)
- All **other parenteral antipsychotics should be ceased** when patients are receiving a course of Acuphase **including PRNs.**
- Acuphase may be mixed in the same syringe with the first dose of flupenthixol decanoate or zuclopenthixol decanoate if a depot is to be initiated.

CAUTION IN PATIENTS WHO:

- are concurrently receiving other antipsychotics
- are sensitive to EPSE's
- have pre-existing cardiac disease

TAKE CARE IF PATIENT IS STRUGGLING (dangerous if given accidentally into vein)

SELECTION OF PATIENTS SUITABLE FOR ACUPHASE

In clinical practice, Acuphase appears to be especially effective in the treatment of:

- Manic relapse
- Drug induced psychosis (notably amphetamine psychosis)
- Aggression/arousal which is difficult to bring under control
- Relapse of chronic schizophrenia.

Figure 2: Alma Street guidelines for the use of Clopixol Acuphase (Zuclopenthixol Acetate).

(produced by DC and DA). The current guidelines, presented in Figures 1 and 2, serve to complement these, and articulate a place for ZA in the management of acute arousal. Like all guidelines, they are not to be seen as prescriptive, and individual clinicians may modify their use of them, according to their own experience, and the precise clinical scenario. Having said this, the Guidelines have been very well received on the Unit, and informal feedback suggests that both medical and nursing staff feel comfortable with them. Furthermore, the Guidelines assist the PICU staff by giving structure and point of reference in their management of those patients with acute arousal.

CONCLUSION

We present here guidelines for the use of Zuclopenthixol acuphase in the management of acute arousal in psychosis. Our clinical experience, the results of serial audits of use of acute arousal medication in our PICU, and informal feedback from medical and nursing staff, suggest that the strategies outlined are easy to follow and are clinically sound and safe. Of course, individual clinical scenarios must always be carefully evaluated, and patients dealt with as individuals rather than there being absolute rigidity about following guidelines, but we believe this is a useful framework in which to operate.

It should be noted that a number of atypical antipsychotic agents have been put into parenteral form, and the availability of such agents is likely to have a major impact on the management of acute arousal in psychosis. Having said this, we are aware of no preparation that will emulate the particular "short-acting depot" properties of ZA, and thus it is likely to continue to have a place in these clinical situations.

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